Upsala J Med Sci 88: 159–168, 1983

Pathophysiology of Acute Myocardial Infarction

G. Baroldi

Institute of Clinical Physiology CNR, Medical School, University of Pisa and Institute of Pathological Anatomy, Medical School, University of Milan, Italy

By definition an acute myocardial infarction (AMI) is an area of myocardial necrosis due to severe reduction or blockage of the nutrient flow. The pathognomonic infarct necrosis - usually termed "coagulation necrosis" - can be reproduced by experimental acute coronary occlusion. Accordingly the pathophysiology of AMI has been related to a variety of coronarogenic (atherosclerotic stenosis, thrombosis, spasm, platelet aggregates, etc.) causes and non coronarogenic (cardiac hypertrophy, aortic stenosis, anemia, etc.) conditions.

However a correct approach should first discriminate between the different nosologic entities associated with AMI and related disorders (angina, sudden death); second verify the cause-effect relation of each factor having in mind that a cause should always result in its effect; third identify all the pathophysiologic mechanisms acting along the course of the natural history (onset, complications, death) of the disease. The first point emphasizes the need to consider separately the so called "ischemic heart disease" (IHD) from other nosologic entities which have different natural history and pathophysiologic background (as dissecting aneurysm or embolism of a main subepicardial coronary artery).

Since the majority of AMI cases belong to IHD entity the preeminent exigency is to focus our attention on its pathophysiology by reviewing the pathogenic significance of the main advocated factors.

Atherosclerotic plaque

The general belief is that the stenosing atherosclerotic plaque is the major ischemic cause. Several facts, however question its cause-effect relation in IHD.

The majority of people with severe coronary atherosclerosis does not present IHD. In 217 patients with coronary atherosclerosis, 171 showed one or more severe stenosis (70% lumen-diameter = 90% lumen-area). Only 40% of the latter had clinical history of IHD and histological documentation of an infarct. When selected groups of IHD patients (AMI first episode (AMIF), AMI second or more episode (AMIS), sudden coronary death cases without previous history of IHD subdivided in "unwarned" (SUD=without prodroma) and "warned (SWD=minor prodroma suggestive a latent IHD) are compared with control groups (non cardiac atherosclerotic patients (NC), normal subjects dying by accident (AD), the percentage distribution of the coronary atherosclerotic damage is as shown in table I.

Table 1. Percentage distribution of the different degree of stenosis lumen reduction%

	69	70-79	80-89	90	70% in 1	2	3 arteries
AMIF (145 cases)	11.0	20.0	31.0	37.2	42.0	33.1	13.1
AMIS (55)	1.8	14.5	20.0	63.6	29.0	40.0	29.0
SUD (106)	23.5	19.8	24.5	32.0	32.0	29.2	15.0
SWD (102)	25.4	7.8	26.4	40.1	18.6	28.4	27.4
NC (100)	34.0	11.0	24.0	31.0	26.0	18.0	22.0
AD (97)	60.8	19.5	13.4	6.1	22.7	13.4	3.1

These figures show: a) too high frequency of severe coronary stenosis, even multiple, in "control" groups; keeping in mind that no significant difference in relation to the length and type (concentric or semilunar) of the stenosis among all groups was found; b) lack of correlation between the degree of coronary damage and IHD. In other words one may have the first IHD episode in presence of minor luminal narrowing or with three or more suboccluded (90%) main arteries (no critical point of stenosis as starting point of the disease); c) pre-existence for month or years of the chronic obstructive damage without evidence of IHD, despite a normal, often stressful, lifestyle. This absence of direct cause-effect relation is confirmed when the extension of myocardial damage is referred to the degree and number of stenosis. In the cases with one or more subocclusion (90%) the majority does not present extensive myocardial fibrosis (Table 2).

Table 2. Frequency of extensive myocardial fibrosis in relation to old occlusion.

	Lumen reduction 90% in			
	1	2	3 arteries	Total
AMI total	65	16	5	89
+ ext. fibrosis	23 (35%)	10 (62.5)	2 (40%)	35 (39%)
SD total	51	22	2	75
+ ext fibrosis	14 (27%)	7 (32%)	1 (50%)	22 (29%)
NC total	27	11	2	40
+ ext. fibrosis	6 (22%)	2 (18%)	1 (50%)	9 (22.5%)
AD total	6	-	-	6
+ ext. fibrosis	- (0.0%)	-	-	- (0.0%)

Furthermore the size of the acute infarct is not related to the number of severe stenosis, as it should be (infarct size proportional to degree of ischemia in turn proportional to the number of severe stenosis (Table 3).

Table 3. Lack of relation between infarct size and number of severe stenosis.

Infarct size %	≤ 69	Stenosis ≥ 70% in 1	2	3 arteries	Total
20	7	39	37	14	97
20	10	39	34	20	103
Total	17	78	71	34	200

All the previous facts suggest two conclusions. First the functional compensatory capability of the collaterals (dramatic increase of collaterals shown post-mortem by tridimensional coronary plastic casts in both IHD patients and controls with identical obstructive damage and by experimental stenosis in dog); and second, the role of mechanisms other than lumen reduction per se in the pathophysiology of IHD.

Thrombosis. The present controversy on the frequency of the occlusive thrombus is based on the assumption that the latter is the cause of the infarct. An assumption apparently confirmed by cineangiographic demonstration of an occlusion in the tributary artery in the majority of acute infarct patients. In our post-mortem experience it became evident that the thrombus, both occlusive and mural, is a multivariant phenomenon which correlates with severe (≥ 70%), long, concentric, "atheromatous" stenosis already by-passed by collaterals and with infarct size.

From these findings the conclusion was that the thrombus is ineffective. A view supported by: a) the uneventful occlusion of an experimental stenosis lasted few days and associated with an enormous increase of collaterals; b) the occurence of thrombi without myocardial infarction; and c) the frequent "silent" occlusion of a stenosis surgically by-passed by vein-graft, the surgical by-pass being equivalent to natural collaterals at very high flow-pressure. These findings support also the view that the thrombus is an event secondary to the regional increase of the peripheral resistance.

This condition may induce the thrombus formation by further blockage of flow within the small residual lumen plus other thrombogenic factors (e.g.loss of fibrinolytic wall activity at the site of "atheromatous" plaque, increased coagulability after tissue necrosis). At present two main mechanisms can be considered in the genesis of such a regional increase. One is the spasm of the tributary artery in its tract distal to the stenosis. Mural thrombi were demonstrated at the level of a severe stenosis in a man who died five hours after the cineangiographic proof of a spasm in the stenosed artery. The other mechanism is the extravascular compression of the intramural arterial system (spasm of these vessels has not yet been definitely proven) due to regional hypercontraction or overdistension of the myocardium (see below different type of necrosis). In particular passive stretching (with paradoxical bulging determined by the intraventricular pressure) is the earliest change of the infarcted area. The highest frequency of thrombi in the largest infarcts (81% in infarcts with a size greater than 40%; 42%; with a size between 10-40%; 20% with a size less than 10%) can be explained by increased peripheral resistance due to extravascular compression in a large area.

The worsening of a stenosis is generally interpreted as cause of increased ischemia. As shown histologically the progression of a plaque is often due to subsequent deposition and organization of mural thrombi. If the thrombi are secondary events in plaques

already by-passed by collaterals, the progression of the latter becomes a meaningless event in ischemic sense. Finally in interpreting the imaging of an occlusion in patients with acute infarct we should keep in mind: a) the cineangiographic occlusion is not synonymous of thrombus, being difficult, if not impossible to discriminate between thrombus and spasm; b)spasm may be associated with and enhanced by thrombus via vasoactive substances released from the latter, when present; c) the well documented fact of a spasm resistent to intracoronary injection of vasodilators; d) the need to distinguish between thrombus and coagulum particularly in relation to the arteriographic vision of "thrombus" dissolution; e) the demonstration of an occlusion after the establishment of the infarct does not prove that the occlusion is the first event.

Other morphologic factors.

In a comparative study - in which different patterns of IHD, healthy people dying by accident and various nosologic "control" conditions were included - no direct cause-effect relation was found between IHD and the many other morphologic causes proposed in the literature. For instance, the frequency and number of vessles occluded by platelet aggregates were identical in SD subjects and healthy controls. In contrast in patients dying from thrombotic thrombocytopenic purpura despite the massive arteriolar occlusion by platelets plus severe obstructive microangiopathy, extreme hemolytic anemia, hemorrhages, neurologic disorders and convulsion (a pool of ischemic and hypoxic factors) there was no clinical and postmortem evidence of IHD. Again, in cor pulmonale, as an extreme example of cardiac hypertrophy, no documentation of infarct necrosis, even in the presence of right coronary occlusion, was found. According to the present status of the art, the approach to the pathophysiology of IHD should inquire the role of spasm and regional disorders of the contractility, why and when they happen, their chronological sequence and their possible relation with other factors which per se seem ineffective. However other facts should be considered, focusing our attention not only on ischemic

mechanisms, but also on the changes seen in the myocardium. Three different types of irreversible myocardial damage can be recognized in relation to the diverse functional stages of the myocardial cell. The latter may die in irreversible relaxation ("atonic" necrosis) or in irreversible hypercontraction ("tetanic" necrosis) or by progressive failure of function ("failing" necrosis).

Each necrosis has a clear-cut morpho-functional pattern, with specific metabolic disorder. In turn this implies a specific pathogenic mechanism for each of them according to the general law that one metabolic disorder always is given the same type of damage, no matter what the cause is. The "atonic" or infarct necrosis is likely to be linked with sudden flow reduction, lasting a determined period of time (at least 20 minutes according to experimental infarct) to induce the pathognomonic dysionism. The other two appear to be non ischemic necrosis in which excess or depletion of catecholamines may have an important role. The constant association of the three types of necrosis in the acute infarct cases and the finding of "tetanic"necrosis as a unique demonstrable lesion in most of the sudden unexpected death cases suggest that in term of complication and death the responsible dysfunctions (dysrhytmias/ventricular fibrillation or failure) are primarily metabolic in nature and not flow depending. In the present era of limitation of infarct size one should be aware that a)any clinical measurement of infarct size may include the non infarct necrosis; and b) the concept of limitation of infarct size in reality means protection of the normal (or better non infarcted) myocardium from a primary metabolic disorder.

KEY REFERENCES

1. Baroldi G.: Acute coronary occlusion as a cause of myocardial infarct and sudden coronary heart death. Am. J. Cardiol. 16: 859, 1965.
2. Baroldi G.: Coronary stenosis: Ischemic or non-ischemic factors? Am. Heart J. 96: (n.2) 139, 1978.
3. Baroldi G.: Coronary thrombosis: facts and beliefs. Am. Heart J. 91: 683, 1976.
4. Baroldi G.: Different types of myocardial necrosis in coronary heart disease: a pathophysiological review of their functional significance. Am. Heart J. 89: 742, 1975.
5. Baroldi G.: Functional Morphology of the Anastomotic Circulation in Human Cardiac Pathology. In BAJUSZ E. and JASMIN G.: "Studies of Functional Morphology: Selected Examples". Meth. Achievm. Exp. Path. 5: 438, Karger, Basel 1971.
6. Baroldi G.: High resistance of the human myocardium to shock and red blood cell aggregation (sludge). Cardiologia 54: 271, 1969.
7. Baroldi G.: Humen myocardial infarction: coronarogenic or noncoronarogenic coagulation necrosis? In BAJUSZ E. and RONA G.: "Recent Advances in Studies on Cardiac Structure and Metabolism". Myocardiology, 1: 388, 1972. University Park Press, Baltimore 1972.
8. Baroldi G.: Lack of correlation between coronary thrombosis and myocardial infarction or sudden "coronary" heart death. Ann. N.Y. Ac. Sci. 156: 504, 1969.
9. Baroldi G.: Limitation of infarct size: theoretical aspects. Proceed. IX World Congr of Cardiol. Moscow 1982 (in press).
10. Baroldi G.: Pathology and mechanism of sudden death. In "The Heart" J.W. Hurst ed., Mc-Graw-Hill Book Co., New York 5th Edition pp. 589, 1982.
11. Baroldi G.: The coronary arteries in chronic Cor pulmonale. Acta Cardiologica 26: 602, 1971.

12. Baroldi G.: The coronary circulation in man. In "Structure and Function of the Circulation". CJ.J. Schwartz ed vol. 2, Plenum Publ. Corp. New York, pp. 77, 1981.
13. Baroldi G., Falzi G. and Mariani F.: Sudden coronary death. A postmortem study in 208 selected cases compared to 97 "control" subjects. Am. Heart J. 98, 20, 1979.
14. Baroldi G. and Manion W.C.: Microcirculatory disturbances and human myocardial infarction. Am Heart J. 74: 171, 1967.
15. Baroldi G., Mantero O. and Scomazzoni G.: The collaterals of the coronary arteries in normal and pathological heart. Circul. Res. 4: 223, 1956.
16. Baroldi G., Milam J.D., Wukasch D.C., Sandiford F.M., Romagnoli A. and Cooley D.A.: Myocardial cell damage in "stone heart". J. Molec. Cell. Cardiol. 6: 395, 1974.
17. Baroldi G., Radice F., Schmid C. and Leone A.: Morphology of acute myocardial infarction in relation to coronary thrombosis. Am. Heart J. 65, 1974.
18. Baroldi G. and Scomazzoni G.: Coronary Circulation in the Normal and Pathologic Heart. U.S. Government Printing Office, Washington D.C. 1967.
19. Baroldi G., Silver M.D., Lixfeld W. and D.C. McGregor: Irreversible myocardial damage resembling catecholamine necrosis secondary to acute coronary occlusion in dogs: its prevention by propranolol. J. Molec. Cell. Cardiol. 9: 687, 1977.
20. Eliot R.S., Baroldi, G. and Leone A.: Necrosy studies in myocardial infarction with minimal or no coronary luminal reduction due to atherosclerosis. Circulation 49: 1127, 1974.
21. Maseri A., L'abbate A., Baroldi G., Chierchia S., Marzilli M., Ballestra A.M., Severi Severi S., Parodi O., Biagini A., Distante A. and Pesola A.: Coronary vasospam as a possible cause of myocardial infarction. N. Engl. J. Med. 299: 1271, 1978.

12. Baroldi G.: The coronary circulation in man. In "Structure and Function of the Circulation". CJ.J. Schwartz ed vol. 2, Plenum Publ. Corp. New York, pp. 77, 1981.
13. Baroldi G., Falzi G. and Mariani F.: Sudden coronary death. A postmortem study in 208 selected cases compared to 97 "control" subjects. Am. Heart J. 98, 20, 1979.
14. Baroldi G. and Manion W.C.: Microcirculatory disturbances and human myocardial infarction. Am Heart J. 74: 171, 1967.
15. Baroldi G., Mantero O. and Scomazzoni G.: The collaterals of the coronary arteries in normal and pathological heart. Circul. Res. 4: 223, 1956.
16. Baroldi G., Milam J.D., Wukasch D.C., Sandiford F.M., Romagnoli A. and Cooley D.A.: Myocardial cell damage in "stone heart". J. Molec. Cell. Cardiol. 6: 395, 1974.
17. Baroldi G., Radice F., Schmid C. and Leone A.: Morphology of acute myocardial infarction in relation to coronary thrombosis. Am. Heart J. 65, 1974.
18. Baroldi G. and Scomazzoni G.: Coronary Circulation in the Normal and Pathologic Heart. U.S. Government Printing Office, Washington D.C. 1967.
19. Baroldi G., Silver M.D., Lixfeld W. and D.C. McGregor: Irreversible myocardial damage resembling catecholamine necrosis secondary to acute coronary occlusion in dogs: its prevention by propranolol. J. Molec. Cell. Cardiol. 9: 687, 1977.
20. Eliot R.S., Baroldi, G. and Leone A.: Necrosy studies in myocardial infarction with minimal or no coronary luminal reduction due to atherosclerosis. Circulation 49: 1127, 1974.
21. Maseri A., L'abbate A., Baroldi G., Chierchia S., Marzilli M., Ballestra A.M., Severi Severi S., Parodi O., Biagini A., Distante A. and Pesola A.: Coronary vasospam as a possible cause of myocardial infarction. N. Engl. J. Med. 299: 1271, 1978.
22. Silver M.D., Baroldi G. and Mariani F.: The relationship between acute occlusive coronary thrombi and myocardial infarction studies in 100 consecutive patients. Circulation 61: 219, 1980.